Major Kidney Clinical Research Studies and Projects Inventory*

Dialysis Access Consortium (DAC)

1. Administrative Data

(a) Name of study/research project and acronym:

Dialysis Access Consortium (DAC)

(b) Type of study/research project (randomized clinical trial, epidemiological study, database, etc.):

Randomized clinical trials: one in fistulas, one in grafts

(c) Funding status (currently funded, study/project completed):

Currently funded

(d) Recruitment status (recruitment completed, currently recruiting):

Recruitment started January 8, 2003

(e) For studies/project currently recruiting: indicate total sample size/ number currently enrolled, anticipated period of recruitment:

Fistula Study: 1,284 patient goal
Graft Study: 1,056 patient goal

(f) Data coordinating center principal investigator contact information (mailing address, phone, fax, and e-mail address):

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(g) Number of recruiting sites, list of principal investigators at recruiting sites and contact information as in (f) above:

Seven (7) clinical centers and principal investigators:

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(h) List of principal investigators at central laboratories/facilities (identify type of central facility) and contact information as in (f) and (g) above:

No central facilities currently

(i) Roster of Data and Safety Monitoring Board/Scientific Advisory Committee or other oversight committee(s):

External Monitoring Committee:

Nathan W. Levin, M.D., Chair, Beth Israel Medical Center
Anatole Besarab, M.D., Henry Ford Hospital
Gerald A. Beathard, M.D.
Glenn Chertow, M.D., M.P.H., Department of Medicine Research
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William McClellan, M.D., MPH, Georgia Medical Care Foundation
Alvaro Mufioz, Ph.D., Johns Hopkins School of Public Health
Catherine Stehman-Breen, M.D., M.S., VA Puget Sound Health Care System

(j) Private-sector support (type of support, e.g., financial, donation of drugs/placebo, etc.):

- Fistula Study: clopidegrol and placebo provided by Bristol-Myers Squibb/Sanofi-Synthelabo, France

- Graft Study: Aggrenox and placebo provided by Boehringer-Ingelheim, Germany

2a. Fistula Study Design

(a) Objective:

The objective of the study is to determine whether clopidogrel reduces the early failure rate of native AV fistulae.

(b) Study design:

The trial is a randomized, double-blind, placebo-controlled multi-center trial with a parallel treatment design. Patients with chronic renal failure who are on chronic hemodialysis or anticipated to begin chronic hemodialysis within six months will be randomized within one calendar day following creation of a new upper extremity native AV fistula to receive either clopidogrel or placebo for six weeks.

Randomization will be on a 1:1 active drug:placebo allocation, and will be stratified by Clinical Center and location of AV fistula (forearm vs. upper arm). Both patients and study personnel will be masked to treatment assignment. The sample size is 1284 patients, to be recruited at seven Clinical Centers over a four-year period. Study drug administration will begin within one calendar day following native AV fistula creation and continue for six weeks following surgery. The primary outcome measure is fistula patency at the end of the six-week study drug administration period. A secondary outcome measure is fistula suitability for dialysis.

(c) Major inclusion criteria:

- Age equal or greater than that at which consent can be obtained without parental involvement (18-21 years depending on state regulations).

- Life expectancy of at least six months.

- Chronic renal failure with anticipated start of hemodialysis within six months of enrollment, or current dialysis dependence.

- Planned creation of native upper extremity AV fistula.

- The patient is not on aspirin, or the patient is on aspirin but has not had a myocardial infarction or a cerebrovascular accident within the past 12 months.

- The patient is expected to stay at a participating dialysis facility for at least 6 months.
- The patient's physician(s) will allow the patient to participate.
- Ability to give informed consent.

(d) Major exclusion criteria:

- Women must not be pregnant, breastfeeding, or plan to be pregnant during the course of the study.
- The presence of ongoing bleeding.
- The presence of a known bleeding disorder (e.g., hemophilia or von Willebrand's disease).
- Recent bleeding episode requiring transfusion within 12 weeks of entry.
- The presence of acute ulcer disease. Acute ulcer disease is defined as a new diagnosis of peptic disease including esophagitis, gastritis, or ulcer or the initiation of treatment with proton pump inhibitors, H2 blockers or therapy for Helicobacter pylon within three months prior to obtaining consent.
- A condition which prohibits discontinuation of anticoagulant drugs, aspirin, or nonsteroidal anti-inflammatory drugs during the six week study drug administration period. Use of heparin during dialysis is allowed.
- Required use of oral or intravenous glucocorticoids at a dose greater than the equivalent of prednisone 15 mg per day during the six week study drug administration period.
- Current unstable angina.
- Required use of clopidogrel.
- Known hypersensitivity to clopidogrel.
- Medical considerations making anti-platelet therapy dangerous.
- Current uncontrolled hypertension with systolic blood pressure in excess of 200 mm Hg or diastolic blood pressure in excess of 115 mm Hg at the time of enrollment.
- Baseline platelet count less than 75,000/mm^3.
- Known advanced liver disease with decompensated cirrhosis, jaundice, ascites or bleeding varices.

- Current problem with substance abuse.
- Concurrent participation in another medical intervention trial.
- Anticipated non-compliance with medical care based on physician judgment.
- Patient refusal.

(e) Description of the intervention(s):

Study drug will consist of identical tablets containing either clopidogrel 75 mg or placebo. The supply of study drug will be provided to the patient following treatment group assignment. Patients will be instructed to take the first dose of study drug by mouth: clopidogrel 300 mg (4 pills) or placebo (4 pills), within one calendar day following fistula creation surgery. After that, the patient will take clopidogrel 75 mg (one pill) or placebo (one pill) daily. Study drug will be continued until six weeks after fistula creation surgery.

(f) Baseline/eligibility visit schedule (number of visits, major assessments):

The baseline evaluation is designed to ensure that subjects meet the inclusion/exclusion criteria, to obtain information regarding demographics, access history, dialysis prescription, and medical history that may affect treatment response and risk of access thrombosis, and to obtain a laboratory evaluation to ensure that patients are not at risk for developing complications of therapy. Data should be collected as close to the time of fistula creation as possible, but no longer than 45 days prior, and should include the following:

- Demographic Data — age, gender, racial/ethnic background.
- Medical History — cause of ESRD, diabetes mellitus, hypertension, myocardial infarction, angina, congestive heart failure, cerebrovascular accident or transient ischemic attack, claudication, amputation, smoking history, deep venous thrombosis or pulmonary embolism, nephrotic syndrome, significant bleeding event within past year, peptic ulcer disease.
- Height and weight (for determination of body mass index).
- Access History — number, type, and location of any previous accesses.
- Dialysis History — date of initiation of chronic dialysis, if currently on dialysis.
- Current Medications

- Blood Pressure (sitting) — For patients already on dialysis, this should be a pre-dialysis, mid-week measurement.

- Laboratory Data — CBC. For patients on dialysis, the blood should be drawn predialysis.

- Laboratory tests should be done no longer than 45 days prior to randomization.

- Quality of life

(g) Follow-up contact schedule (frequency, type of visit/phone, in-clinic, major assessments):

Six weeks after fistula creation:

- Fistula Anatomy — date of surgery, site of anastomosis (e.g., wrist, elbow), inflow artery, outflow vein.

- Fistula Patency —presence of bruit throughout systole and diastole ≥8 cm proximal to the arteriovenous anastomosis

- Current Medications

- Intercurrent /Adverse Events — drug reactions, side effects, hospitalizations, death, access procedures (fistulogram, angioplasty, thrombectomy, conversion to graft, ligation of draining veins), abnormal laboratory values, or other complications. The occurrence of any such events should be reported as close to the time the event occurred as possible; however, the review at this study visit should minimize the possibility that such events go unrecognized or unreported. Patients will be instructed at enrollment to inform study personnel immediately if a bleeding event occurs.

- If dialysis was initiated via the new fistula prior to this six-week study visit the date of initiation of dialysis should be recorded.

- Procedures performed on fistula (fistulogram, angioplasty, thrombectomy, conversion to graft, ligation of draining veins), and dates of such procedures.

- Study Drug Use — reason for and duration of study drug interruption. Remaining study drug should be returned at this visit and pill count performed.

- Quality of life

For patients with fistula thrombosis and no restoration of patency during the six week study drug administration period, all of the above data will be collected at the earlier of the following: six weeks after fistula creation or at the end of study participation (30 days after discontinuation of study drug).

Follow-up data after six week study visit:
After the six-week study visit, contact will be made by the study coordinator with study subjects, their physicians, their dialysis units, and other sources on a monthly basis to capture data on interim events and to ascertain secondary outcomes. The data to be collected include the following:

- Date of first cannulation of fistula.
- Date at which fistula is used for four weeks of consecutive dialysis treatments.
- Minimum dialysis machine blood flow rate during the 12 dialysis sessions prior to study completion.
- The minimum blood flow rate should be determined from the blood flow measurements recorded after the first hour and before the last 15 minutes of the dialysis session. Study completion will occur five months after fistula creation for patients who are on dialysis at the time of fistula creation or start dialysis within 4 months of fistula creation. Study completion will occur four weeks after dialysis initiation for patients who start dialysis > 4 months after fistula creation.
- Procedures performed on fistula (fistulogram, angioplasty, thrombectomy, conversion to graft, ligation of draining veins), and dates of such procedures.
- For patients not on chronic dialysis prior to creation of the fistula — date of first dialysis.
- Intercurrent/Adverse Events - bleeding events and hospitalizations during the 30 days following end of study drug administration period. Death during the period of study participation.
- Quality of life
- For patients with fistula thrombosis and no restoration of patency during the six-week study drug administration period, quality of life data is collected as indicated in item
- Data collection after study participation has ended will include hospitalization data and mortality data obtained from national databases while the study is on-going and for up to five years after the study has ended.

(h) Primary outcome, secondary outcomes:

Primary Outcome:

Unless the reason for discontinuation of the study drug was fistula thrombosis, the fistula patency outcome will be ascertained at six weeks after creation of the fistula

even if the study drug was discontinued before that date. To allow patients to complete study participation within 30 days of stopping the study drug because of fistula thrombosis, the fistula patency outcome assessment may be completed at any time within the 30 day period. Fistula patency will be determined by physical examination of the fistula performed by trained study personnel. The fistula will be classified as patent if a bruit is present throughout systole and diastole. The bruit must be detectable along the vein at least 8 centimeters proximal to the arteriovenous anastomosis. In a quality control subset of patients the outcome will be independently assessed by at least one trained member of the study team and a second person.

Secondary outcome:

Fistula suitability for dialysis. Suitability for dialysis is defined as the ability to use the fistula for dialysis for at least four weeks and obtain a minimal nominal dialysis blood flow of 300 ml/min. To meet the 300 ml/min dialysis blood flow criterion, all blood flow measurements recorded after the first hour and before the last 15 minutes of the dialysis session must be ≥300 ml/min. In order to distinguish fistula inadequacy from poor dialysis needle placement, which might occasionally occur and result in low blood flow, the requirement for nominal blood flow of ≥300 ml/min must be met during at least 8 dialysis treatments during the four-week period. Fistulae suitable for dialysis will include those modified radiologically or surgically.

Radiological modification may include percutaneous balloon angioplasty of stenoses, or pharmacological or mechanical thrombolysis. Surgical modification may include thrombectomy, or revision of the arteriovenous anastomosis as long as the same artery and vein are used. The fistula suitability outcome will be ascertained during the fourth month after creation of the fistula for patients on dialysis before creation of the fistula.

For patients who have not initiated dialysis at the time of fistula creation, fistula suitability will be ascertained during the fourth month after fistula creation if dialysis is initiated within four months of fistula creation, or during the first month after dialysis initiation if dialysis is initiated more than four months after fistula creation. Initial unsuccessful use of the fistula will not preclude attainment of the fistula suitability outcome as long as suitability criteria are met during the ascertainment period described above.

Suitability for dialysis criteria is defined above except when the fistula cannot be modified radiologically or surgically. Modified fistulae will be considered to have failed on the date of modification.

(i) Brief summary of power estimates used to justify sample size/duration, including critical assumptions (i.e., effect-size estimates, estimated event rates or rate of change in outcome measure):

From review of the literature, it is estimated that fistula thrombosis at six weeks (primary outcome) will occur in 25% of patients treated with a placebo, and failure to achieve

fistula suitability for dialysis (secondary outcome) will occur in 40% of patients treated with a placebo. To detect a 30% reduction in fistula thrombosis rate with 85% power and a two-sided-alpha level of 0.05, 1,284 patients are required (642 in each treatment group) assuming a 5% loss to follow-up rate, a 3% treatment drop-in rate, and a 3% treatment drop-out rate. This sample size also includes a slight upward adjustment (2.7%) to account for the O'Brien-Fleming stopping rule suggested by the Steering Committee. Under a fixed sample size design, the sample size of 1,284 would provide approximately 80% power to detect a 20% reduction in failure to achieve fistula suitability for dialysis.

2b. Graft Study Design

(a) Objective:

To determine whether Aggrenox (dipyridamole and aspirin) (BoehringerIngelheim) prolongs primary unassisted patency in newly created arteriovenous grafts.

(b) Study design:

The study will be a randomized double-blind, placebo-controlled multi-center trial of Aggrenox compared to a placebo for the prevention of access failure in patients who receive a new arteriovenous graft. Eligible subjects will be enrolled and baseline data collected before the placement of a new graft. After successful placement of the graft, subjects will be randomized with equal allocation to therapy with either Aggrenox 1 capsule twice a day or a matched placebo. For randomization, subjects will be stratified by the Clinical Center and whether the graft placement is in the lower arm or at another site (e.g., upper arm or leg) and whether or not the patient is using an ACE inhibitor or angiotensin receptor blocker at enrollment. The study medication will be started within two days of the access surgery and continued until the primary endpoint.

The primary outcome will be primary unassisted patency, defined as the time from randomization until the composite endpoint of thrombosis or any access procedure required to maintain or restore access function (subsequently referred to as the first access event).

Predefined secondary outcomes include (1) the time from randomization to site failure, (2) time from randomization to death, and (3) time from randomization to the composite outcome of site failure or death.

The study participants will be followed monthly to measure access flow rate and record access related complications, adverse drug reactions, hospitalizations, and medication compliance until the primary endpoint is reached. Monthly measurement of access flow rate will be used to detect a hemodynamically significant stenosis before it leads to access thrombosis. A drop in monthly access flow rate that meets pre-specified limits will trigger angiographic evaluation and repair of the access if a 50% or greater stenosis is observed.

The study drug and active monitoring will be discontinued when the primary endpoint is reached. Further follow-up will be limited to determining whether total access site failure or death occurred prior to study closeout and if so, the time of that event. It is anticipated that the study will enroll a total of 1,056 subjects over three years with a minimum additional follow-up of one year (for a total study duration of four years) to have an 85% power to detect a 25% treatment effect. This projected sample size will incorporate a statistical stopping rule, which will allow the External Advisory Committee to terminate the study early if therapy with Aggrenox is proven to be effective or if it becomes clear that the null hypothesis is unlikely to be disproved.

(c) Major inclusion criteria:

- Age equal or greater than that at which consent can be obtained without parental involvement (18-21 years depending on state regulations).
- Life expectancy of at least six months.
- Chronic renal failure with anticipated start of hemodialysis within six months of enrollment, or current dialysis-dependence.
- A new or planned AV graft placed in any location for the purpose of hemodialysis. (Any type of graft material and any configuration of the access is acceptable).
- The patient is expected to stay at a participating dialysis facility for at least 6 months.
- The patient's physician(s) will allow the patient to participate.
- Ability to give informed consent.

(d) Major exclusion criteria:

- Women must not be pregnant, breastfeeding, or plan to be pregnant during the course of the study.
- The presence of ongoing bleeding.
- The presence of a known bleeding disorder (e.g., hemophilia or von Willebrand's disease).
- Recent bleeding episode requiring transfusion within 12 weeks of entry.
- The presence of acute ulcer disease (Acute ulcer disease is defined as a new diagnosis of peptic disease including esophagitis, gastritis, or ulcer or the initiation of treatment with proton pump inhibitors, H2 blockers or therapy for Helicobacter pylori within three months prior to obtaining consent).

- Known allergy or adverse reaction to Aggrenox or any of its study components (dipyridamole and aspirin).
- Required use of warfarin, dipyridamole, non-steroidal anti-inflammatory drugs, or other anti-platelet agents other than aspirin.
- Current uncontrolled hypertension with systolic blood pressure in excess of 200 mm Hg or diastolic blood pressure in excess of 115 mm Hg.
- Baseline platelet count of less than 75,000/mm^3.
- Known advanced liver disease with decompensated cirrhosis, jaundice, ascites or bleeding varices.
- Current problem with substance abuse.
- Concurrent participation in another medical intervention trial.
- Anticipated non-compliance with medical care based on physician judgment.
- Patient refusal.

(e) Description of the intervention(s):

The first dose of study medication should be administered starting within two days of access creation. The Aggrenox or matched placebo should be taken as one pill twice a day. Assuming there are no reasons for early termination of the study medication, the study medication should be administered throughout the duration of the study until the primary endpoint occurs or study termination.

(f) Baseline/eligibility visit schedule (number of visits, major assessments):

The baseline evaluation is designed to: (1) ensure that subjects meet the inclusion/exclusion criteria, (2) obtain information regarding demographics, access history, medications, and medical history that may affect treatment response and risk of access failure, and (3) obtain information on medical history and laboratory tests to ensure that patients are not at risk for developing complications of therapy.

Data should be collected as close to the time of graft creation as possible, but no longer than 45 days prior to it. Data collection should include the following:

- Patient identification — demographic information (age, gender, race)
- Patient's mailing address for study medication. If no suitable home address, medication will be mailed to the dialysis unit to provide to the patient

- Date of enrollment
- Date of ESRD; start date for hemodialysis
- Cause of ESRD (diabetes, hypertension, polycystic kidney disease, glomerulonephritis, interstitial nephritis, hereditary nephritis, or other)
- Access history: (a) prior arteriovenous access attempts — number, type, location, date(s) placed; (b) prior central catheter placements (subclavian or int. jugular) — yes/no; right, left or both
- Current central catheter — type, site, date placed
- Diagnoses (history of diabetes (duration, nephropathy, retinopathy, neuropathy), hypertension (duration), vascular disease (myocardial infarction, CABG, CHF, angina, stroke, TIAs, peripheral vascular disease, amputations), coagulopathy, or hyperlipidemia
- List of current medications
- Tobacco use (how much, age at start, currently smoking (yes/no), if not, when habit stopped)
- Quality of life questionnaire
- Blood pressure and pulse — pre-dialysis and in sitting position
- Height and weight
- Periodontal disease (no obvious cavities or gingivitis, cavities or gingivitis, or edentulous)
- Examine arms to note scars and evaluate number and location of any current functional accesses and previously failed access sites
- Look for presence of current central catheter—Note type and location.
- Baseline biochemical measurements—most recent within the last 45 days, record date CBC (hemoglobin, platelet count), and albumin.

(g) Follow-up contact schedule (frequency, type of visit/phone, in-clinic, major assessments):

First monthly visit:

At the first visit after creation of the access data on the type of graft material used and the location and configuration of the graft will be collected. In addition, the date of surgery and the surgeon will be confirmed. The date of first cannulation of the access for dialysis will be recorded as soon as it is available.

All monthly visits:

- Access recirculation and access blood flow within first two hours of dialysis (see Manual of Operations)
- Blood pressure (sitting) predialysis (from chart) and at time of access blood flow
- Person doing needle insertion (patient or nurse).
- Problems with needle insertion in the last month (hematomas, multiple needle sticks, failed insertions)
- Access related events.
- Access related procedures — indication, date of procedure, outcome
- Hospitalizations — primary and secondary diagnosis, dates of admission and discharge
- Compliance with study medications as assessed by patient interview and monthly pill count. Subjects will be asked to return pill bottles of study medication each month.
- Current medications.
- Monthly dialysis lab tests — serum albumin, hemoglobin, hematocrit, pre- and post-BUN, calcium, phosphorus. PTH when available every third month.
- For incident patients not yet on dialysis the patency of the access will be determined by the presence of an audible bruit or a palpable thrill in the graft.
- Adverse event monitoring.

Monthly adverse event monitoring:

Adverse events will be recorded at the monthly visits. Subjects will be asked the following questions:

- Have you had any problems with your study medication? Describe them.
- Have you had any hospitalizations? When and what was the reason?

- Have you had any other new significant health problems? Describe them.

- Have you had any episodes of significant bleeding?

- Are you having any gastrointestinal symptoms such as heartburn or abdominal pain?

The responses to all these questions will be recorded and an assessment will be made as to whether the event is related to the study medication. For any hospitalizations or emergency room visits, the medical record will be reviewed to determine the cause of the visit and whether it was likely related to the study medication. Particular attention will be given to whether a bleeding event precipitated the visit or hospitalization.

For patients that might be questionable historians, the dialysis nurse caring for the patient will be asked whether they are aware of any adverse events, hospitalizations, or transfusions that have occurred in the preceding month. In addition, the patient dialysis logs will be examined to determine if the patient missed any sessions and the patient will be asked the reason for the absence. Serious adverse events are those that result in any of the following outcomes: death, a life-threatening adverse experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly or birth defect. All serious adverse events will be reported to the DCC within 24 hours of study personnel learning of the event.

Every third month:

Response to quality of life questions will be obtained.

(h) Primary outcome, secondary outcomes:

Primary Outcome:

The primary outcome will be primary, unassisted patency defined as the time from randomization until the first occurrence of either of the following:

- Thrombosis

- An access procedure performed or recommended to restore patency including angioplasty, thrombolysis, thrombectomy, or any surgical modification of the graft.

It is stipulated that access surgery done to modify the access because of a steal syndrome or congestive heart failure occurring within the first 30 days after creation of the access will not be considered an event for the primary composite outcome. However, loss of access function for any reason will be considered a primary outcome. The primary endpoint will also be considered to occur if the subject is found to have a ≥50% access stenosis by angiography for which an intervention is recommended but refused.

For patients who are undergoing regular hemodialysis, failure to use the new graft by six weeks after access creation will be considered access site failure and the study will be terminated. For incident patients not yet on hemodialysis, patency of the access will be determined by monthly assessment of the graft for the presence of an audible bruit or a palpable thrill. Loss of both of these findings will be considered to be the primary event and the date of the endpoint will be the date of ascertainment by the study coordinator.

The primary endpoint will not include diagnostic studies (e.g., angiogram or ultrasound) that reveal a stenosis <50%.

Secondary Outcome:

Cumulative Patency—Time to Complete Access Site Failure:
Complete loss of a functional access site is an outcome of major clinical importance. It is not economically feasible to continue the study drug and intensive monthly data collection for the duration needed for an adequately powered study of site failure. However, it is important to track this outcome at the closeout of the study to see if the trend is consistent with the effect seen for the study drug in the main trial. For this analysis, cumulative patency is the time from randomization to complete loss of the access site for dialysis regardless of the number of interventions required to restore or maintain patency.

Loss of the access site is defined by the need to place a new access using new arteriotomy and venotomy incisions or by the abandonment of the prior access as defined by the need for a central venous dialysis catheter for a period of ≥ 1 month. Operationally, the need

for a new arteriotomy and venotomy sites will be detected by the need for a completely new site for the placement of the access. (Note that in most instances, a chart review should not be needed to determine this endpoint). Procedures used to prolong the function of the access at the current site such as resection and replacement of part of the graft or changing just the site of the venous anastomosis will not be considered site failure).

It is anticipated that a pharmacological agent that prolongs primary, unassisted patency will also prolong cumulative patency even if the drug is stopped at the primary endpoint. The median cumulative patency in a control population without active flow monitoring and angioplasty is expected to be about two years. An active access surveillance program will prolong access survival in the control population beyond two years but the exact duration is not well defined in the literature.

Patient Survival:

It is important that the study drug not produce any adverse consequences that might be worse than the measured outcome. Aspirin contained in Aggrenox is expected to cause an increase in minor and major bleeding events but is not expected to increase serious or fatal bleeding events. On the other hand, aspirin is known to decrease the rate of arterial thrombotic events in high risk populations. Given the high rate of cardiovascular death in the hemodialysis population, aspirin might actually improve overall patient survival. Due to the importance of this issue, time from randomization to death has been designated as a secondary outcome variable. However, it is recognized that the power of the study to detect a treatment effect on mortality is limited.

(i) Brief summary of power estimates used to justify sample size/duration, including critical assumptions (i.e., effect-size estimates, estimated event rates or rate of change in outcome measure):

Sample Size Calculations:

The rationale for each of the assumptions used to calculate the required sample size for the study is outlined below. All of the calculations are based on the primary outcome of primary unassisted patency. The power calculations assume a constant hazard rate for the primary outcome, with a one-year probability of access failure in the control group of 0.54. The calculations further assume an annual loss to follow-up of 22%, an annual drop-out rate of 15%, and an annual drop-in rate of 1%.

Under the suggested predefined stopping rule (see below), a total of 1,056 subjects will be required to have a 85% power to detect a 25% reduction in the rate of the primary outcome for Aggrenox compared to placebo. Under the assumption of a constant hazard rate, this corresponds to a 33% increase in median primary unassisted patency from 10.70 to 14.28 months. Assuming that there will be a total of seven Clinical Centers with a total of 1,136 new grafts placed per year, an enrollment rate of 31.0% would allow patient accrual to be completed by three years and the total study duration would not exceed four years. With the recommended stopping

rule, the expected study duration will be slightly under three years under both the null hypothesis of no treatment effect and the research hypothesis of a 25% benefit of Aggrenox.

Event Rate:

Primary unassisted patency rates for upper extremity grafts vary with patient selection, surgical expertise as well as site and configuration of the graft. Recent studies that mirror the circumstances of this study reveal one-year primary unassisted patency rates of between 23% to 49%. Due to limits in ascertaining early access failures, data from the USRDS likely underestimates overall access failure rates. The remaining studies report one-year primary unassisted patency rates of between 23% to 43%. Since study patients will likely do somewhat better than average a one-year primary unassisted patency rate of 46% was determined for the primary power calculations (i.e., a one-year probability of access failure of 0.54).

Effect Size:

The study by Sreedhara (1994) found a 50% effect size for dipyridamole alone and 27% for dipyridamole plus aspirin to decrease thrombosis in new grafts. No other controlled trial of dipyridamole to prevent hemodialysis access failure has been reported. However, long-term follow-up of vein grafts used for coronary artery bypass have also found an effect size of 41% for aspirin plus dipyridamole to decrease the percent of veins that have a stenosis compared to placebo. Tempering these data is one retrospective report suggesting no effect of dipyridamole to prevent hemodialysis graft failure. Looking at the effect of dipyridamole in the secondary prevention of occlusive arterial vascular disease (i.e., myocardial infarction and stroke), most studies have used a combination of aspirin and dipyridamole. The effect size in these studies was between 18% and 36%. However, in most studies the addition of dipyridamole was not shown to improve the outcome over aspirin alone.

In contrast, in a large randomized, placebo-controlled double-blind study for secondary prevention of ischemic stroke involving 6,602 patients, dipyridamole (200 mg bid; n=1654) was found to decrease the risk of stroke by 16% and the combination of aspirin plus dipyridamole (n=1650) reduced risk by 37%. In this study, low-dose aspirin (25 mg bid) alone reduced the risk by 18%, which is somewhat less than studies using a higher dose of aspirin. Nevertheless, this large study demonstrates that dipyridamole alone is effective for secondary stroke prevention and the combination medication Aggrenox is better.

Finally, with regard to restenosis after a vascular procedure, the data published to date would suggest no benefit of using lower doses of immediate release dipyridamole. However, as discussed above these studies may not be relevant to angioplasty of venous lesions and the time-averaged concentration of dipyridamole would be much lower than that provided by Aggrenox. We are not aware of any clinical trials of Aggrenox after angioplasty in humans. However, dipyridamole has been effective in experimental

models to prevent restenosis after angioplasty. Based on these studies and on clinical estimates of what effect size would constitute a meaningful result, an effect size of 25% has been hypothesized for the primary outcome.

Subject Loss or Modality Transfer:

Based on the data from the HEMO Study, we anticipate that the rate of patient death, transfer to another treatment modality, or loss to follow-up will be 22%.

Drop-in and Drop-out:

Based on prior experience in large scale clinical trials, the annual rate of drop-outs (patients randomized to the Aggrenox arm who stop taking active drug) was assumed to be 15%. The annual rate of drop-ins (patients randomized to the placebo arm who receive Aggrenox or a related drug) was assumed to be 1%.

3. Data and Biological Sample Resources

(a) Biological samples collected in ongoing studies/research projects (specify the type of sample, e.g., blood, urine, etc., the amount, and the point in the study when samples were collected, e.g., baseline visit #1, baseline visit #2, follow-up visit #1; specify months after randomization/study entry):

No biological samples are being collected. Blood may be collected in an ancillary study.

(b) Biological samples currently in storage from completed trials (grid showing sample collection time, type of sample, amount and number of study participants sample was collected from, and physical location of where the samples are stored):

No stored samples currently.

(c) Brief summary of typical informed consent provisions (template informed consent form acceptable), including major variables in participant consents, if applicable (e.g., "use for other studies or not", "allow genetic studies or not."). Does consent include use of samples in other studies that are not part of the main study?

Consents currently do not contain language about stored specimens.

(d) Data collected (grid of data collection by time/clinic visit with specificity on the type of information collected, e.g., quality of life with SF-MOS 36, measurement of kidney function by GFR, serum creatinine measurement, etc.):

See Appendix A: Form Table of Contents

Fistula Study: see Appendix B for forms completion schedule

Graft Study: see Appendix C for forms completion schedule

(e) Any provisions for distributing resources outside of the study? What is the sharing plan?

No current procedures for sharing but data and any stored samples will become part of the NIDDK Repository. Procedures for access to NIDDK Repository data/samples are not known at this time.

4. Ancillary Studies

(a) Process and contact person (name, address, phone, fax, and e-mail address) for application to perform ancillary studies:

Ancillary study applications should be sent to:

Gerald Beck, Ph.D.
Department of Biostatistics and Epidemiology, Wb4
Cleveland Clinic Foundation
9500 Euclid Avenue
Cleveland, OH 44195

Ancillary study applications will be reviewed by the Publications and Ancillary Studies Committee.

(b) List of ancillary studies approved, completed and ongoing (including source of funding and amount):

None

5. List of Publications and Presentations (full citations, also note manuscripts in progress)

Dember L, Kaufman J, Beck G, Dixon B, Gassman I, Greene T, Himmelfarb J, Hunsicker L, Kusek J, Middleton J, Schwab S, Feldman H and the DAC Study Group. Dialysis Access Consortium (DAC) Trial Design: Clopidogrel prevention of early AV fistula thrombosis. Journal of the American Society of Nephrology 13:229A, 2002.

Dixon B, Greene T, Beck G, Dember LM, Gassman J, Himmelfarb J, Hunsicker LG, Kaufman J, Kusek J, Middleton JP, Schwab SJ, Feldman HI and the DAC Study Group. Dialysis Access Consortium (DAC) trial design: Sustained-release dipyridamole plus aspirin to prevent graft failure. Journal of the American Society of Nephrology 13:232A, 2002.

Appendix A. Forms—Table of Contents

Form #	Form Name	Revision Date
301F	Fistula Study: Screening Form	01/06/03
302F	Fistula Study: Baseline Drop-out Form	01/03/03
304F	Fistula Study: Patency Form	01/23/03
305F	Fistula Study: Suitability Form	01/06/03
306F	Fistula Study: Pill Dispensing Form	01/22/03
308	Surgeons Intraoperative Form (for ancillary studies)	09/05/02
309F	For the EAC: Documentation of incident fistulas at this unit for patients who were not screened	Not done
311G	Graft Study: Screening Form	12/04/02
312G	Graft Study: Baseline Drop-out Form	01/03/03
313G	Graft Study: First Post Surgical Visit Form for Graft Study	11/26/02
314G	Graft Study: Monthly Graft Related Follow up Visit Form	01/03/03
315G	Graft Study: Pill Dispensing Form at Randomization	01/22/03
316G	Graft Study Pill Counting / Dispensing Form	01/22/03
317G	Graft Study: Quarterly Form	01/03/03
319G	For the EAC: Documentation of incident grafts at this unit for patients who were not screened	Not done
322FG	Patient Family, Employment and Income Form	11/21/02
324FG	Baseline Medication Tracking Form	01/20/03
331FG	Demographics, Comorbidity, and Dialysis History Form	12/04/02
333FG	Visit Form	01/03/03
334FG	Follow-up Medication Tracking Form	01/20/03
335FG	Temporary Discontinuation of Therapy Form	11/21/02
336FG	Permanent Discontinuation of Therapy Form	12/04/02
337FG	Cessation Committee: Review of Permanent Discontinuation of Therapy Form	11/21/02
341FG	Quality of Life Assessment (English Version)	01/03/03
351FG	Local Biochemistry Laboratory Data Form	01/03/03
352F	Fistula Study: Access Repair / Access Event Procedure	11/26/02
353G	Graft Study: Ultrasound Monitoring Form: Access Blood Flow Surveillance	01/06/03
354G	Graft Study: Diagnostic Procedure (Fistulogram, Angiogram, Venogram) Form	11/21/02
355G	Graft Study: Access Repair / Access Event Procedure (Angioplasty and other procedures) Form	01/03/03
356G	Graft Study: Site Failure, Thrombosis (End Point) Form	12/04/02
360	FG Clinical Center Hospitalization Notification Form	11/25/02
361	FG Clinical Center Hospitalization Form	01/06/03
362	FG Hospitalization Review From	Not done
363	FG Transfusion/Bleeding Episodes Form	01/03/03

364	FG Persistent Disability / Incapacity Form	11/26/02
365	FG Life Threatening Event Form	11/26/02
366	FG Birth Defect Event Form	11/25/02
371	FG Clinical Center Death Notification Form	11/25/02
372	FG Clinical Center Death Review Form	11/25/02
373	FG Committee Death Review Form	11/25/02
382	FG Patient Transfer Form	01/03/03
390	FG Annual Check on Vital Status for Inactive Patients Form	Not done

Surveys

1001	DAC Study — Dialysis Unit Survey	04/26/02
1004	DAC Study — Surgeon Identification Form	06/26/02
1005	DAC Study — Certification for Flow Monitoring	06/14/02

Reports and On-Line Applications

R1	Fistula Study Eligibility for Randomization Report	
R2	Graft Study Eligibility for Randomization Report	
R3	DCC "This patient needs a fistulography" Report	
R5	Serious Adverse Event	09/05/02
Al	Graft Study Randomization On-Line Application	01/03/03
A2	Fistula Study Randomization On-Line Application	01/03/03

Appendix B. DAC Fistula Study Forms Completion Schedule

Table 1. DAC Fistula Study Baseline Forms							
Time	**Forms**						
	301	322	324	331	333	341	351
Before enrollment	X	X	X	X	X	X	X

Baseline

Fax signed consent with patient ID, namecode, and study name to the DCC with the signature blocked out. The patient must be randomized within 90 days of the date the consent is signed or you will need to get a new consent.

If the patient has already consented and you know that he or she is ineligible, complete Forms 301 and 331. You do not fill out a drop-out form.

If labs and forms are 45 days old, redo baseline forms except for Forms 322, 331 and 341 (which should be reviewed for accuracy). These forms will have to be updated after 90 days.

Forms 301, 322, 324, 331, 333, and 341 may be entered in any order. When results for the blood work are received, the Local Biochemistry Laboratory Form 351 may be entered.

After the forms are entered, run the on-line eligibility report. It will indicate if the DCC has received the consent, if the patient is eligible, and the last day the patient can be randomized without having to get additional data.

Other forms that are completed as needed are: Form 360 (Hospitalization Notification), Form 361 (Clinical Center Hospitalization), Form 363 (Transfusion/Bleeding Episodes), Form 365 (Life Threatening Event), Form 366 (Birth Defect Event), Form 371 (Clinical Center Death Notification) and Form 372 (Clinical Center Death Review).

Complete Form 302 (Fistula Study Drop-out Form) if the patient will not be randomized.

Table 2. DAC Fistula Study Follow-Up Forms						
Time	**Forms**					
	304	305	306	333	334	341
At randomization			X			
One day after randomization: compliance	Enter date on form					
Two-week call: compliance & safety	Enter date on form					
Four-week call: compliance& safety	Enter date on form					
Six-week visit	X (complete and enter form)			X	X	X
30 days after drug d/c: safety call						
Monthly calls to check on start of dialysis						
Month 5*		X				X

Other Follow-Up Forms As Needed

If drug is discontinued at any time after randomization: Form 335 (Temporary Discontinuation of Therapy) or Form 336 (Permanent Discontinuation of Therapy).

If the patient needs another bottle of study drug, fill out Form 306.

At the 2-week call, 4-week call, 30-day safety call, and monthly calls if needed:

Form 333 (Visit)
Form 352 (Access Repair/Access Event Procedure)
Form 360 (Clinical Center Hospitalization Notification)
Form 361 (Clinical Center Hospitalization)
Form 363 (Transfusion/Bleeding Episodes)
Form 364 (Persistent Disability/Incapacity-only after at least 3 months)
Form 365 (Life Threatening Event)
Form 366 (Birth Defect Event)
Form 371 (Clinical Center Death Notification)
Form 372 (Clinical Center Death Review)
Form 382 (Patient Transfer).

At the 6-week visit if needed:

Form 352, 360, 361, 363, 364, 365, 366, 371, 372

***At month 5 (Forms 305 & 341):**

If the patient was on chronic dialysis before the fistula surgery or if the patient was not on chronic dialysis before the fistula surgery but dialysis was initiated within four months of fistula creation, forms 305 and 341 are completed at month 5.

If dialysis was initiated more than four months after fistula creation, Forms 305 and 341 are completed after four weeks of consecutive dialysis treatment.

For patients with fistula thrombosis and no restoration of patency during the six-week study drug administration period—complete Forms 304, 333, 334, 336, and 341 at the earlier of the following: six weeks after fistula creation or at the end of study participation (30 days after discontinuation of study drug).

After study participation ends:

Before the end of the study, complete the Form 390 (Annual Vital Status Check).

Appendix C. DAC Graft Study Forms Completion Schedule

Table 1. DAC Graft Study Baseline Forms Completion Schedule							
Time	**Forms**						
	311	322	324	331	333	341	351
Before enrollment	X	X	X	X	X	X	X

Fax signed consent with patient ID, namecode and study name to the DCC with signature blocked out. The patient must be randomized within 90 days of the date the consent is signed, or you will need to get a new consent.

If the patient has already consented and you know that he/she is ineligible, complete Forms 311 and 331. You do not fill out a drop-out form.

If labs and forms are 45 days old, redo baseline forms except for Form 322, 331 and 341 (which should be reviewed for accuracy). These forms will have to be updated after 90 days.

Forms 311, 322, 324, 331, 333, and 341 may be entered in any order. When results for the blood work are received, the Local Biochemistry Laboratory Form 351 may be entered.

After the forms are entered, run the on-line eligibility report. It will indicate if the DCC has received the consent, if the patient is eligible, and the last day the patient can be randomized without having to get additional data.

Other forms that are completed as needed are: Form 360 (Hospitalization Notification), Form 361 (Clinical Center Hospitalization), Form 363 (Transfusion/Bleeding Episodes), Form *365* (Life Threatening Event), Form 366 (Birth Defect Event), Form 371 (Clinical Center Death Notification) and Form 372 (Clinical Center Death Review).

Complete Form 312 (Graft Study Drop-out Form) if the patient will not be randomized.

Table 5: DAC Graft Study Follow-Up Forms										
Time	**Forms**									
	313	314	315	316	317	333	334	341	351	353
At randomization			X							
Month 1	X	X	X	X		X	X	X	X	If access used for dialysis
Month 3 through 1st follow-up visit after primary end-point		X	X	X		X	X		X	X
Quarterly follow-up					X			X		
30 days after drug discontinued: safety call										

Other forms as needed:

If drug is discontinued at any time after randomization: Form 335 (Temporary Discontinuation of Therapy) or Form 336 (Permanent Discontinuation of Therapy).

At monthly follow-ups through first follow-up after primary endpoint, if needed:

Form 354 (Diagnostic Procedure [Fistulogram, Angiogram, Venogram])
Form 355 (Access Repair/Access Event Procedure [Angioplasty and other procedures])
Form 356 (Site Failure, Thrombosis [End Point])
Form 360 (Clinical Center Hospitalization Notification)
Form 361 (Clinical Center Hospitalization), Form 363 (Transfusion/Bleeding Episodes)
Form 364 (Persistent Disability/Incapacity-only after at least 3 months)
Form 365 (Life Threatening Event)
Form 366 (Birth Defect Event)
Form 371 (Clinical Center Death Notification)
Form 372 (Clinical Center Death Review)
Form 382 (Patient Transfer).

At the 30-day safety call after the drug is discontinued, if needed:

Forms 333, 354, 355, 356, 360, 361, 363, 364, 365, 366, 371, 372

After study participation ends:

Before the end of the study, complete the Form 390 (Annual Vital Status Check).